REMARKS

Claims 19, 23-42, and 54-57 are pending with Claims 19, 25, 27, 33, 35, and 37 being amended. Claims 25, 27, 33, 35, and 37 have been amended to correct typographical and formatting errors. No new matter has been added with the amendments. Support for the amendments can be found in the claims as filed and in the specification, for example at [0062].

Claim Objections

Claim 33 was objected to on grounds that the terms "the" and "a" were both placed in front of the term "skin sensor" in line 2 of the claim. Applicant has amended Claim 33 to remove the term "the."

Rejections under 35 U.S.C. § 112, first paragraph

Claims 19, 23-42, and 54-57 were rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. The Examiner states that the limitation "as compared to the intensity and/or wavelength that is observed in the absence of the metabolite or analyte" in claim 19 is not sufficiently supported by disclosure as originally filed, and is thus considered to be new matter. The Examiner elaborates that the disclosure as originally filed only supports comparing the intensity and/or wavelength that is observed using the known stoichiometric relationship between the fluorescence spectrum of the reporter and the metabolite parameter or analyte concentration.

Applicants have amended this phrase in the claims to clarify what is being claimed, such that the rejection is overcome. Claim 19 now reads, in pertinent part, "the wavelength and/or intensity of fluorescence emission or absorbance of said reporter dye varies in proportion to a change in concentration of a metabolite or analyte." The amendment is supported by the specification and does not constitute new matter. Paragraph [0062] of the specification states:

> This invention most specifically relates to small molecule metabolite reporters (SMMRs) that indicate the rate and quantity of glycolysis occurring within the living cell loci. The detailed spectral changes noted as direct and indirect metabolic reporters include: variation in fluorescence emission intensity and lifetime . . . These measureable changes vary in direct proportion to the changes in concentrations of metabolite molecules within the physical proximity of associated extracellular and intracellular structures.

Applicant notes that the changes in fluorescence emission intensity and lifetime vary proportionally in response to changes in concentration of metabolite molecules, including a change between zero and non-zero concentration.

Rejections under 35 U.S.C. § 103

Claims 19, 23-26, 28, 29, 30-36, 38, 39, and 40-42 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,040,194 to Chick et al. in view of U.S. Patent No. 6,485,703 to Cote et al. and U.S. Patent No. 6,377,721 to Walt et al. The Examiner notes that Chick teaches an in vivo method and sensor for detecting an analyte, but is silent with regard to intracellular concentrations of analytes, and does not teach a specific time period for application or the use of BCECF as a molecular size attachment.

The Examiner argues, however, that it would have been obvious to monitor intracellular concentrations of analytes using the method of Chick in view of Cote and Walt. Cote teaches the importance of monitoring both intra- and extra-cellular analytes, and particularly intracellular glucose. Walt teaches the acetoxymethyl ester form of BCECF as an intracellular dye. The Examiner further argues that there would be a reasonable expectation of success because Cote teaches that a method for monitoring intracellular concentration may involve using different sized particles and because Chick teaches that selectivity can be accomplished using molecular size. Additionally, the Examiner argues that one of ordinary skill in the art would be motivated to use the acetoxymethyl ester form of BCECF disclosed in Walt as an intracellular dye in the method of Chick because Chick also discloses BCECF as a pH indicator.

Cote teaches using polymer hydrogel particles of two different sizes to monitor intra- and extra-cellular analytes. In particular, Cote teaches that the smaller size can be taken up by cells to allow measurement of intracellular analyte concentrations. Cote also teaches that it is important to monitor intracellular glucose in diabetic patients because, "the acute problems related to diabetes are correlated to intracellular glucose levels" (col. 24, lines 56-59). Chick is silent as to the size of the reagents used in its sensor and how one might alter the size of the reagents. The Examiner points to column 16, lines 46-47 of Chick as providing a teaching that selectivity can be accomplished using molecular size. Applicant notes, however, that the referenced paragraph refers to the size of the analyte and not the size of the fluorescence reagent, and is accomplished by altering the pore size of a semipermeable membrane so that only analytes

of a certain maximum size can pass through to interact with the fluorescence reagent contained within the membrane of the implantable sensor. As stated in Chick, "The sensor could also be provided with a semipermeable membrane that allows analyte to diffuse freely into and out of the sensor, but not the fluorescence reagents. Selectivity can be based upon molecular size or upon electrostatic or chemical characteristics" (col. 16, lines 45-49).

Accordingly, Chick teaches that varying the permeability of a membrane can effect size-selective movement of analytes into and out of an implanted sensor. Chick does not, however, provide any teaching as to how one might alter the disclosed fluorescence reagents or substitute them with other fluorescence reagents so as to allow the fluorescence reagents to have a size and chemistry that would allow it to diffuse across a cellular membrane to allow intracellular monitoring.

The Examiner argues that this proposition is unconvincing and cites paragraph [0061] in Applicant's specification for the proposition that, "it is well known that specific dyes bind to cellular structures and allow imaging and anatomical/histological studies of intracellular structures." In addition, the Examiner argues that one of ordinary skill in the art would have been motivated to use the acetoxymethyl ester form of BCECF disclosed in Walt as an intracellular dye in the method of Chick.

Applicant acknowledges that the referenced paragraph explains that specific dyes have been known to allow intracellular structural imaging or characterization of cellular metabolism. However, the referenced paragraph goes on to state that, "no specific fluorophores have been named . . . for in vivo, non-invasive elucidation of metabolic pathways for any medical applications in general . . ." Similarly, Walt teaches the use of dyes such as the acetoxymethyl ester form of BCECF as assays for cell viability. Walt does not teach the use of such dyes for the purpose of monitoring live human keratinocyte metabolic processes, such as glycolysis, or to determine the concentration of metabolites or analytes related to such processes. Therefore, although some intracellular dyes may have been known in the art, no specific intracellular fluorophores have been described for in vivo monitoring of metabolite or analyte concentration or metabolic processes. Accordingly, a person of ordinary skill in the art would not have a reasonable expectation of success in trying to combine the teachings of Chick with those of Cote or Walt to obtain the presently claimed invention.

Claims 27 and 37, which are directed in part to the monitoring of lactate as the specific metabolite or analyte, were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Chick, Cote, and Walt as applied previously to claims 19, 23-26, 28, 29, 30-36, 38, 39, and 40-42, and further in view of U.S. Patent No. 5,972,199 to Heller et al. The Examiner acknowledges that the teachings of Chick, Cote, and Walt combined do not specifically disclose lactate as a metabolite to be measured. However, the Examiner argues that Heller teaches the importance of assaying lactate in certain fields such as medicine. Thus, the Examiner argues that one of ordinary skill in the art would have been motivated to use the methods of Chick to monitor levels of lactate in a patient. Additionally, the Examiner argues that one of ordinary skill in the art would have had a reasonable expectation of success because Chick teaches inorganic or organic ions generally as suitable analytes.

Heller teaches electrochemical sensors which are capable of measuring biochemicals in body fluids (col. 1, lines 61-63). Although Heller discloses monitoring lactate concentrations in body fluids, Heller does not disclose the intracellular monitoring of lactate or other biochemicals. As explained above, the combination of Chick, Cote, and Walt fails to describe intracellular reporters for use in in vivo monitoring of metabolite or analyte concentrations or metabolic processes. Accordingly, a person of ordinary skill in the art would not have a reasonable expectation of success in combining the teachings of Chick, Cote, Walt, and Heller to obtain the invention as claimed.

Double Patenting Rejections

Claims 19, 23-42, and 54-57 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22-25, 31-50, 53, and 54 of copending Application No. 11/349,731. Without acquiescing to such rejection, Applicant notes that a Terminal Disclaimer was filed on November 7, 2007 in connection with copending Application No. 11/349,731.

In view of the foregoing, it is respectfully asserted that Claims 19 and 33 are patentable. Furthermore, all claims depending directly or indirectly from Claims 19 and 33, particularly claims 27 and 37, are also patentable for at least the same reasons as discussed above for their respective independent claim, and also because each claim recites a novel and unobvious combination of elements.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: 1/31/08.

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